

CA 2578050	A1	20060323	CA 2005-2578050	20050721
WO 2006031291	A2	20060323	WO 2005-US25831	20050721
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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EP 1786902	A2	20070523	EP 2005-790917	20050721
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IN 2007DN02576	A	20070803	IN 2007-DN2576	20070405
KR 2007064619	A	20070621	KR 2007-708112	20070410
PRIORITY APPLN. INFO.:				
US 2002-428535P P 20021122				
US 2003-464217P P 20030419				
US 2003-718986 A2 20031121				
US 2004-561749P P 20040413				
US 2004-580084P P 20040616				
US 2004-939262 A 20040910				
WO 2005-US25831 W 20050721				

AB Fusion proteins that use a glycosaminoglycan-binding domain to bind antibacterial proteins to a cell surface are described for the treatment of microbial infection, especially influenza. Use of the glycosaminoglycan-binding domains targets the protein to the surface of epithelial cells, and this binds the therapeutic domain to the cell surface to prevent infection of the target cell by a pathogen such as an influenza virus. The glycosaminoglycan-binding anchoring domain may be from a mammalian protein, such as human platelet factor 4, interleukin 8, antithrombin III, or apolipoprotein E. The therapeutic domain may be an enzyme, such as a sialidase, or a protease inhibitor for a host enzyme involved in processing a viral protein. Examples of protease inhibitors are aprotinin, leupeptin, soybean proteinase inhibitor, e-aminocaproic acid, or n-p-tosyl-L-lysine.

L1 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:470946 HCAPLUS Full-text

DOCUMENT NUMBER: 141:33763

TITLE: Broad spectrum antivirals comprising a target cell-anchoring GAG-binding domain fused with protease inhibitor or sialidase, for treatment and preventing influenza

INVENTOR(S): Yu, Mang; Fang, Fang

PATENT ASSIGNEE(S): USA

SOURCE: PCT Int. Appl., 75 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 2004047735	A2	20040610	WO 2003-US37158	20031121

WO 2004047735 A3 20040923

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO,
NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ,
TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
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TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2506526 A1 20040610 CA 2003-2506526 20031121

AU 2003294401 A1 20040618 AU 2003-294401 20031121

AU 2003294401 B2 20071129

EP 1567185 A2 20050831 EP 2003-789884 20031121

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

CN 1729013 A 20060201 CN 2003-80107241 20031121

JP 2006508193 T 20060309 JP 2005-510377 20031121

IN 2005DN02646 A 20070126 IN 2005-DN2646 20050616

PRIORITY APPLN. INFO.: US 2002-428535P P 20021122

US 2003-464217P P 20030419

WO 2003-US37158 W 20031121

AB The present invention provides new protein-based compns. and methods for preventing and treating pathogen infection, particularly influenza. The compds. have at least one N-terminal or C-terminal anchoring domain that anchors the compound to the surface of a target epithelial cell, and at least one therapeutic domain that can act extracellularly to prevent infection of the target cell by a pathogen, such as a influenza virus. The said anchoring domain comprises a GAG-binding motif from a mammalian protein, such as human platelet factor 4, interleukin 8, antithrombin III, apolipoprotein E, angio-associated cell migratory protein (AAMP), or amphiregulin. The said therapeutic domain comprises enzyme, such as sialidase, or protease inhibitor for host enzyme involved in processing a viral protein. Examples of protease inhibitors are aprotinin, leupeptin, soybean proteinase inhibitor, e-aminocaproic acid, or n-p-tosyl-L-lysine.

L1 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1998:128718 HCAPLUS Full-text

DOCUMENT NUMBER: 128:216171

TITLE: Caprine mucopolysaccharidosis-IIID: clinical, biochemical, morphological and immunohistochemical characteristics

AUTHOR(S): Jones, Margaret Z.; Alroy, Joseph; Boyer, Philip J.; Cavanagh, Kevin T.; Johnson, Kent; Gage, Douglas; Vorro, Joseph; Render, James A.; Common, Ralph S.; Leedle, Robert A.; Lowrie, Charles; Sharp, Peter; Liour, Shyh-Shyurng; Levene, Beverly; Hoard, Heidi; Lucas, Rebecca; Hopwood, John J.

CORPORATE SOURCE: Department of Pathology, Michigan State University, East Lansing, MI, 48824, USA

SOURCE: Journal of Neuropathology and Experimental Neurology (1998), 57(2), 148-157

CODEN: JNENAD; ISSN: 0022-3069

PUBLISHER: American Association of Neuropathologists, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Several animal models have been developed for the mucopolysaccharidoses (MPSs), a group of lysosomal storage disorders caused by lysosomal hydrolase

deficiencies that disrupt the catabolism of glycosaminoglycans (GAG). Among the MPS, the MPS-III (Sanfilippo) syndromes lacked an animal counterpart until recently. In this investigation of caprine MPS-IIID, the clin., biochem., morphol., and immunohistochem. studies revealed severe and mild phenotypes like those observed in human MPS III syndromes. Both forms of caprine MPS IIID result from a nonsense mutation and consequent deficiency of lysosomal N-acetylglucosamine 6-sulfatase (G6S) activity and are associated with tissue storage and urinary excretion of heparan sulfate (HS). Using special stains, immunohistochem., and electron microscopy, secondary lysosomes filled with GAG were identified in most tissues from affected goats. Primary neuronal accumulation of HS and the secondary storage of gangliosides were observed in the central nervous system (CNS) of these animals. In addition, morphol. changes in the CNS such as neuritic expansions and other neuronal alterations that may have functional significance were also seen. The spectrum of lesions was greater in the severe form of caprine MPS IIID and included mild cartilaginous, bony, and corneal lesions. The more pronounced neuropathic deficits in the severe form were partly related to a greater extent of CNS dysmyelination. These findings demonstrate that caprine MPS IIID is a suitable animal model for the investigation of therapeutic strategies for MPS III syndromes.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 4 OF 6 BIOTECHDS COPYRIGHT 2008 THE THOMSON CORP. on STN

ACCESSION NUMBER: 2007-24900 BIOTECHDS Full-text

TITLE: Making a protein-based composition comprises adding counterion to a solution containing the protein in an aqueous solvent, adding an organic solvent to the solution, and gradually cooling the solution; recombinant sialidase fusion protein production for use in disease therapy

AUTHOR: MALAKNOV M P; FANG F

PATENT ASSIGNEE: MALAKNOV M P; FANG F

PATENT INFO: US 2007190163 16 Aug 2007

APPLICATION INFO: US 2007-657812 24 Jan 2007

PRIORITY INFO: US 2007-657812 24 Jan 2007; US 2006-762002 24 Jan 2006

DOCUMENT TYPE: Patent

LANGUAGE: English

OTHER SOURCE: WPI: 2007-699628 [65]

AB DERWENT ABSTRACT:

NOVELTY - Making a protein-based composition comprises (a) adding a counterion to a solution containing the protein in an aqueous solvent; (b) adding an organic solvent to the solution; and (c) gradually cooling the solution to a temperature below 25degreesC, where a composition containing microparticles comprising the protein is formed, where steps (a), (b), and (c) are performed simultaneously, sequentially, intermittently, or in any order.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are: (1) a composition, comprising microparticles of a sialidase or a sialidase fusion protein; and (2) an article of manufacture, comprising the composition, a packaging material for the composition and a label that indicates that the composition is for a therapeutic indication. BIOTECHNOLOGY - Preferred Method: Steps (a) and (b) are performed simultaneously or sequentially in any order, followed by step (c). Steps (a), (b) and (c) are performed sequentially in the order: (a), then (b), then (c). The organic solvent is miscible or partially miscible with the aqueous solvent. The method further comprises after step (c), separating the microparticles from the solution to remove components other than the microparticles, where the composition consists essentially of the microparticles comprising the protein, where the separation is effected by sedimentation or by filtration or by freeze-drying. The organic solvent is

selected from aliphatic alcohols (preferred), aromatic alcohols, chloroform, dimethyl chloride, polyhydric sugar alcohols, aromatic hydrocarbons, aldehydes, ketones, esters, ethers, dioxanes, alkanes, alkenes, conjugated dienes, dichloromethane, acetonitrile, ethyl acetate, polyols, polyimides, polyesters, polyaldehydes, or their mixtures, where the aliphatic alcohol is isopropanol. The counterion is selected from among an anionic compound (preferred), a cationic compound, or a zwitterionic compound, where the anionic compound is glycine, sodium citrate, sodium sulfate (preferred), zinc sulfate, magnesium sulfate, potassium sulfate, or calcium sulfate. The microparticles are obtained by precipitation, by phase separation or by colloid formation. The pH of the solution is at or below the pI of the protein, where the pH of the solution is 4.0 or 4.0 to 9.0 or 9.0; 4.5 or 4.5 to 8.0 or 8.0; 4.5 or 4.5 to 6.5 or 6.5; 4.5 or 4.5 to 5.5 or 5.5. The protein is selected from sialidases, sialidase fusion proteins, proteases, protease inhibitors (preferred), cytokines, insulin, human growth hormone, calcitonin, recombinant human DNase, interferons, or parathyroid hormone, where the protease inhibitor is human protease inhibitor 8 (PI8). The protein is a sialidase fusion protein. The sialidase fusion protein contains a catalytic domain of a sialidase and an anchoring domain, where the catalytic domain of the sialidase is the only portion of the sialidase in the sialidase fusion protein. The sialidase is an *Actinomyces viscosus* sialidase (preferred), a *Clostridium perfringens* sialidase, an *Arthrobacter ureafaciens* sialidase, a *Micromonospora viridifaciens* sialidase, a human Neu2 sialidase or a human Neu4 sialidase. The amino acid sequence of the catalytic domain contains the sequence of amino acid residues beginning at any of the amino acids from amino acid 270 to amino acid 290 and ending at any of the amino acids from amino acid 665 to amino acid 901 of the sequence of amino acids set forth in SEQ ID NO: 1. The sequence of the sialidase catalytic domain contains the sequence of amino acid residues set forth in SEQ ID NO: 2. The sequence of the catalytic domain comprises the sequence of amino acid residues beginning at amino acid 274 and ending at amino acid 681 of the sequence of amino acids set forth in SEQ ID NO: 1, where the sequence of the catalytic domain comprises the sequence of amino acid residues beginning at amino acid 274 and ending at amino acid 666 of the sequence of amino acids set forth in SEQ ID NO: 1. The sequence of the catalytic domain comprises the sequence of amino acids beginning at amino acid 290 and ending at amino acid 681 of the sequence of amino acids set forth in SEQ ID NO: 1. The anchoring domain that is a glycosaminoglycan (GAG)-binding domain, where the GAG-binding domain is GAG-binding domain of human platelet factor 4, the GAG-binding domain of human interleukin 8, the GAG-binding domain of human antithrombin III, the GAG-binding domain of human apoprotein E, the GAG-binding domain of human angio-associated migratory protein and the GAG-binding domain of human amphiregulin, where the amino acid sequence of the GAG-binding domain contains the sequence of amino acid residues set forth in SEQ ID NO: 3-8, where the amino acid sequence of the GAG-binding domain contains the sequence of amino acid residues set forth in SEQ ID NO: 8. The amino acid sequence of the sialidase fusion protein contains the sequence of amino acid residues set forth in SEQ ID NO: 9-14 or 17. The resulting microparticle composition further comprises acid-resistant coating agents, protease-resistant coating agents, enteric coating agents, bulking agents, excipients, inactive ingredients, stability enhancers, taste and/or odor modifiers or masking agents, vitamins, therapeutic agents, anti-oxidants, immunomodulators, trans-membrane transport modifiers, anti-caking agents, chitosans or flowability enhancers. The amount of protein in the microparticles relative to the total amount of protein in the solution of step (a) is 80% or 80% to greater than 99% or 99%. The temperature is 4degreesC to -45degreesC. The resulting protein based composition has a shelf life of one week to 1 month, 1-6 months, six months to one year, 1-2 years, or 2-5 years at 55degreesC or below. The solution and/or the resulting composition further comprises an active agent selected from antidiabetics,

anticonvulsants, analgesics, antiparkinsons, anti-inflammatories, calcium antagonists, anesthetics, antimicrobials, antimalarials, antiparasitics, antihypertensives, antihistamines, antipyretics, alpha-adrenergic agonists, alpha-blockers, biocides, bactericides, bronchial dilators, beta-adrenergic blocking drugs, contraceptives, cardiovascular drugs, calcium channel inhibitors, depressants, diagnostics, diuretics, electrolytes, enzymes, hypnotics, hormones, hypoglycemics, hyperglycemics, muscle contractants, muscle relaxants, neoplastics, glycoproteins, nucleoproteins, lipoproteins, ophthalmics, psychic energizers, sedatives, steroids, sympathomimetics, parasympathomimetics, tranquilizers, urinary tract drugs, vaccines, vaginal drugs, vitamins, minerals, nonsteroidal anti-inflammatory drugs, angiotensin converting enzymes, polynucleotides, polypeptides, or polysaccharides, where the active agent is selected from among antidiabetics, enzymes, hormones, vitamins, minerals, or nutritional supplements. The moisture content of the microparticles is adjusted where at least 90% of the activity of the protein is retained after storage for six months to 1 year at 25degreesC. The moisture content of the microparticles is adjusted where at least 90% of the microparticles are not aggregated after storage for six months to 1 year at 25degreesC. The moisture content of the microparticles is 6-12%, preferably 7-10.5%. The gradual cooling is at 0.01degreesC/min or 0.01degreesC/min to 20degreesC/min or 20degreesC/min, preferably 1degreesC /min. The size of the microparticles is 0.001 microns or 0.001 microns to 50 microns or 50 microns, preferably 1.0 microns to 2.0, 3.0, 4.0 or 5.0 microns. Preferred Article of Manufacture: The therapeutic indication is influenza. The article further comprises an inhaler for pulmonary administration of the composition, where the inhaler is a dry powder inhaler, a metered dose inhaler or an electrostatic delivery device. ACTIVITY - Neuroprotective; Respiratory-Gen; Immunosuppressive; Muscular-Gen; Gynecological; Gastrointestinal-Gen; Metabolic; Cardiovascular-Gen; Nephrotropic; Cytostatic; Antiinflammatory; Antimicrobial. No biological data given.

MECHANISM OF ACTION - None Given.

USE - The method is useful for making a protein-based composition, where the composition is useful for treating diseases and disorders including neural disorders, respiratory disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, digestive disorders, metabolic disorders, cardiovascular disorders, renal disorders, proliferative disorders, cancerous diseases, inflammation, or infectious diseases. ADMINISTRATION - Dosage is 0.5-60 mg/kg. The composition is for oral administration (e.g. ingestion), intravenous, intranasal, parenteral, pulmonary, subcutaneous, ophthalmic or intramuscular administration, or for inhalation (claimed).

ADVANTAGE - The present invention provides a method for producing protein and other macromolecular microparticles that does not require complex or specialized equipment and that produces uniform-sized microparticles for delivery; provides a method of producing micro- particles that contain high concentrations of the protein or macromolecule relative to other components, that are stable and maintain their activity for long periods of time when stored at ambient temperature and that do not contain a significant amount of denatured protein; provides a method of producing microparticles of proteins and other macromolecules where substantially all of the protein or macromolecule in the starting material is recovered in the microparticle formulation, with minimal loss; and provides microparticles of proteins or other macromolecules containing these properties for administration, for example, as a therapeutic or nutritional supplement. EXAMPLE - No suitable example given. (63 pages)

least one therapeutic domain, and one anchoring domain, each comprising a peptide or protein, useful for treating or preventing pathogen infection, e.g. influenza; involving vector-mediated gene transfer and expression in host cell for use in recombinant vaccine preparation

AUTHOR: YU M; FANG F
PATENT ASSIGNEE: YU M; FANG F
PATENT INFO: WO 2004047735 10 Jun 2004
APPLICATION INFO: WO 2003-US37158 21 Nov 2003
PRIORITY INFO: US 2003-464217 19 Apr 2003; US 2002-428535 22 Nov 2002
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2004-441066 [41]

AB DERWENT ABSTRACT:

NOVELTY - A protein-based composition for preventing or treating infection by a pathogen, comprises a compound having at least one therapeutic domain (an enzyme) comprising a peptide or protein, and at least one anchoring domain comprising a peptide or protein.

DETAILED DESCRIPTION - A protein-based composition for preventing or treating infection by a pathogen, comprises a compound having at least one therapeutic domain comprising a peptide or protein, and at least one anchoring domain comprising a peptide or protein. The therapeutic domain has at least one extracellular activity that can prevent the infection of a target cell by a pathogen, and the anchoring domain can bind at or near the surface of a eukaryotic cell. BIOTECHNOLOGY - Preferred Composition: The anchoring domain can bind at or near the surface of an epithelial or endothelial cell, preferably at or near the surface of an epithelial cell, where the anchoring domain binds an epithelial cell surface molecule. The epithelial cell surface molecule is a glycosaminoglycan, and anchoring domain can bind heparin or heparin sulfate, where the anchoring domain is a peptide comprising a GAG-binding amino acid sequence of a naturally-occurring protein, or a sequence that is substantially homologous to the GAG-binding sequence of a naturally-occurring protein. The peptide comprises the GAG-binding amino acid sequence of a mammalian protein, preferably a human protein. The peptide comprises an amino acid sequence substantially homologous to an amino acid sequence comprising 24, 27, 34, 34, 12 or 21 amino acids (SEQ ID NO: 2-7, respectively) given in the specification. The peptide comprises the GAG-binding amino acid sequence of human platelet factor 4 (SEQ ID NO: 2), human interleukin 8 (SEQ ID NO: 3), human antithrombin III (SEQ ID NO: 4), human apoprotein E (SEQ ID NO: 5), human angio-associated migratory protein (SEQ ID NO: 6), or human amphiregulin (SEQ ID NO: 7). The pathogen is a virus, such as an influenza virus, specifically an influenza A or an influenza B virus. The therapeutic domain comprises a protease inhibitor that inhibits an enzyme involved in processing a viral protein, where the enzyme involved in processing a viral protein is a host enzyme. The protease inhibitor is a serine protease inhibitor, preferably aprotinin, leupeptin, soybean protease inhibitor, e-aminocaproic acid, or n-p-tosyl-L-lysine. The anchoring domain is N-terminal to the therapeutic domain. There may also be at least 2 anchoring domains, where one of the 2 anchoring domains is N-terminal to the therapeutic domain, and at least one of the 2 anchoring domains is C-terminal to the one therapeutic domain. The 2 anchoring domains and at least one or two therapeutic domains are connected by peptide linkers. The therapeutic domain is an enzyme or its active portion, preferably a sialidase substantially homologous to at least a portion of at least one viral, bacterial or eukaryotic sialidase. The sialidase is substantially homologous to at least a portion of at least one bacterial sialidase, which is substantially homologous to at least a portion of a bacterial sialidase that can cleave a sialic acid alpha, 2-6 linkage and a sialic acid alpha 2-3 linkage. The sialidase comprises or is substantially homologous to at least a portion of the sequence of *Vibrio cholerae* sialidase, *Clostridium perfringens*

sialidase, *Actinomyces viscosus* sialidase, or *Micromonospora viridifaciens* sialidase. The sialidase is substantially homologous to at least a portion of NEU1, NEU3, NEU2 (SEQ ID NO: 8), or NEU4 (SEQ ID NO: 9). The composition further comprises at least one peptide linker that links the anchoring domain to the therapeutic domain, where the peptide linker comprises 1-100 amino acids, and comprises at least one glycine residue. Preferably, the peptide linker comprises the sequence (GGGGS)_n, where n = a whole number from 1-20, particularly from 1-12. The formulation comprising the composition is formulated as a spray or as an inhalant. In using a sialidase to prevent or impede infection by a pathogen, the sialidase is substantially homologous to at least a portion of at least one viral, bacterial or eukaryotic sialidase. The subject is a human subject, and the sialidase is substantially homologous to at least a portion of at least one human sialidase. The sialidase is substantially homologous to at least a portion of NEU2 (379 amino acids, SEQ ID NO: 8), or NEU4 (424 amino acids, SEQ ID NO: 9). The composition comprising the sialidase is applied using a nasal spray, preferably an inhaler.

ACTIVITY - Virucide. Test details are described but no biological data given.
MECHANISM OF ACTION - Vaccine.

USE - The composition is useful for treating or preventing pathogen infection, particularly influenza infection (claimed). ADMINISTRATION - The composition is applied using a nasal spray, preferably an inhaler, 1-4 times a day (claimed). The composition may also be administered topically, parenterally, intravenously, subcutaneously, intramuscularly, colonically, rectally, nasally or intraperitoneally, and at a dose of 1 ng/kg-10 mg/kg, preferably 100 ng/100 microg/kg.

ADVANTAGE - The new protein-based composition overcomes disadvantages of current therapies for treating or preventing pathogen infection, e.g. difficult to provide in a timely manner, undesirable effects, and can lead to drug-resistant pathogen strains. EXAMPLE - Experimental protocols are described but no results are given. (75 pages)

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FILE 'MEDLINE, HCAPLUS, BIOSIS, BIOTECHDS, SCISEARCH, EMBASE' ENTERED AT 12:01:27 ON 26 FEB 2008

L1 6 S THERAPEUTIC AND SIALIDASE AND (GAG OR GLOCOSAMINOGLYCAN)
L2 5 DUP REM L1 (1 DUPLICATE REMOVED)

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FULL ESTIMATED COST	62.07	62.28
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	-2.40	-2.40

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